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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/815,557	ENGELHARDT ET AL.	
	Examiner	Art Unit	
	Kevin K. Hill, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-53* is/are pending in the application.

4a) Of the above claim(s) *8-12,14,17-19,21,22 and 24-53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-7,13,15,16,20 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Applicant has elected with traverse the invention of Group I, claims 1-13 and 15-32, drawn to a method of identifying one or more agents with therapeutic activity to treat one or more symptoms of a disease which is associate with aberrant expression or activity of epithelial sodium channels (ENaC),

Within Group I, Applicant has further elected the restricted subgroup "IA", Claims 1-9, 13, 15-23 and 28-32, drawn to a method of identifying an agent with dual therapeutic activity in mammalian cells.

Within Group IA, Applicant has elected the following species:

i) the physiological agent category, antibiotic, as recited in Claim 16,

ii) the physiological agent compound , doxil, as recited in Claim 20. Upon further examination of the subject matter, the Examiner has extended the species to include doxorubicin.

iii) the cellular functionality, wherein the agent modulates transcription of a molecule that regulates ENaC transcription, as recited in Claim 23,

iv) the virus type, adeno-associated virus, as recited in Claim 4,

v) the selected transcriptional agent activity, wherein the agent is effective to decrease the level or amount of transcription of one or more subunits of ENaC, as recited in Claim 7, and

vi) the mammalian cell type species, human, as recited in Claim 15.

Amendments

Applicant's response and amendments, filed August 23, 2007, to the prior Office Action is acknowledged. Applicant has cancelled Claim 3, withdrawn Claims 8-12, 14, 17-19, 21-22 and 24-53, and amended Claims 1-2, 4, 13, 15-16, 20 and 23.

Claims 8-12, 14, 17-19, 21-22 and 24-53 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 1-2, 4-7, 13, 15-16, 20 and 23 are under consideration.

Examiner's Note

Unless otherwise indicated, previous objections/rejections that have been rendered moot in view of the amendment will not be reiterated. The arguments in the August 23, 2007 response will be addressed to the extent that they apply to current rejection(s).

Priority

Applicant's claim for the benefit of a prior-filed application parent provisional applications 60/459,323, filed March 31, 2003 and 60/512,347, filed October 16, 2003 under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged.

Oath/Declaration

The Oath and Declaration filed August 23, 2007 is acknowledged and accepted.

Drawings

The Replacement Drawings filed August 23, 2007 are acknowledged and accepted.

Specification

1. **The disclosure stands objected to because of the following informalities**:

35 U.S.C. 112, first paragraph, requires the specification to be written in "full, clear, concise, and exact terms." The specification is replete with terms which are not clear, concise and exact. The specification should be revised carefully in order to comply with 35 U.S.C. 112, first paragraph. Examples of some unclear, inexact or verbose terms used in the specification are: The specification uses the terms "doxorubicin", "doxyrubicin" and "doxil", each of which may be abbreviated as "DOX". However, the specification discloses that doxil could not be confirmed to be bioavailable to cell culture cells (pg 71, lines 22-24), and that "intranasally doxil-treated mice did better than the doxorubicin-treated animals" (pg 101, lines 7-9). Thus, one of ordinary skill in the art would reasonably conclude that the functional ability(ies) of "doxorubicin", "doxyrubicin" and "doxil", are not identical in effect. As such, it is imperative that "doxorubicin", "doxyrubicin" and "doxil", and use thereof, be clearly and explicitly identified throughout the disclosure.

A) The use of trademark compositions has been noted in this application. The specification uses the term "Miglyol" (pg 43, lines 19-21) which is registered trademarks. Trademarked compositions should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. Applicant is advised to review the specification to correctly identify all trademark compositions.

B) The units (DF*) categorizing the results in Table 2 (pgs 75-76) are not defined in the table or disclosed in the working example that describes the experiment used to acquire the data (Example 3), thus prohibiting a meaningful evaluation on the merits.

C) The specification does not adequately identify the "DOX" compound whose effects are graphed in Figures 5-10 (pgs 13-15).

Appropriate correction is required.

Response to Amendments

Applicant argues that the terms "doxorubicin" and "doxyrubicin" are synonymous, and that the active ingredient in DOXIL® is doxorubicin. Furthermore, in the context of the particular data disclosed in the specification (*in vitro* versus *in vivo*), the use of "DOX" in the specification is clear.

Applicant's argument(s) has been fully considered, but is not persuasive.

With respect to A), Applicant has not addressed "Miglyol".

With respect to B), Applicant has not explained the definition of "DF*".

With respect to C), in the absence of explicitly pointing out where (page, line) the distinctions between doxycycline and DOXIL® are taught for each experiment so as to provide clear correspondence with the corresponding data shown in the respective figures, the instant argument is incomplete and unpersuasive. The specification discloses that DOXIL® could not be confirmed to be bioavailable to cell culture cells (pg 80, lines 17-18; pg 82, lines 2-4), and that "intranasally DOXIL®-treated mice did better than the doxorubicin-treated animals" (pg 110, lines 17-19). Thus, one of ordinary skill in the art would reasonably conclude that the functional ability(ies) of "doxorubicin" or "doxyrubicin" and DOXIL®, are not identical in effect. As such, it is imperative that "doxorubicin" or "doxyrubicin" and DOXIL® be clearly and explicitly identified throughout the disclosure.

Claim Objections

2. **Claims 13, 15-16, 20 and 23 stand objected to under 37 CFR 1.75(c)** as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. Furthermore, the claims recite dependency on claims (Claims 10, 11 and 12) drawn to non-elected inventions. See MPEP § 608.01(n).

Appropriate correction is required.

Response to Amendment

While Applicant has deleted dependency on claims 10-12, the claims have not been amended to refer to other claims in the alternative only. See, for example, claim 4.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. **Claims 1-2, 4-7, 13, 15-16, 20 and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.** The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a new rejection.

With respect to claim 1, and claims dependent thereon, the claimed invention is directed to a method to identify one or more agents with dual therapeutic activity, the method comprising the step of selecting one or more agents which inhibits expression or activity of amiloride-sensitive epithelial sodium channels (ENaC) having α, β and γ subunits of ENaC, wherein the selected agent is effective to decrease the level or amount of transcription of one or more subunits of ENaC.

With respect to claim 2, and claims dependent thereon, the claimed invention is directed to a method to identify one or more agents with dual therapeutic activity, the method comprising the step of selecting one or more agents which enhances the transduction of a viral gene therapy vector, wherein said agent which enhances the transduction of a viral gene therapy vector also possesses the functional property of modulating the transcription of one or more molecules that can regulate ENaC transcription.

At issue for the purpose of written description requirements is the lack of written description for those agents possessing the required functional properties and those mammalian cells having aberrant expression or activity of amiloride-sensitive epithelial sodium channels (ENaC) having α, β and γ subunits of ENaC.

> *Vas-cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification

should "clearly allow persons of ordinary skill in the art to recognize that (he or she) invented what is claimed." (See *Vas-cath* at page 1116).

The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see *In re Shokal* 113USPQ283(CCPA1957); *Purdue Pharma L.P. vs Faulding Inc.* 56 USPQ2nd 1481 (CAFC 2000).

In analyzing whether the written description requirement is met for agent genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, doxorubicin is the only species whose complete structure is disclosed to possess the functional property of inhibiting the expression of amiloride-sensitive epithelial sodium channels (ENaC) having α, β and γ subunits of ENaC, wherein the selected agent is effective to decrease the level or amount of transcription of the ENaC γ-subunit. The specification discloses that doxorubicin increases the CpG methylation of the γ-ENaC gene promoter (pg 15, Figure 11; pg 93, lines 7-30). It is noted that the specification discloses that it is not known if doxorubicin inhibits long-term ENaC activity through increases in α- or β-ENaC subunit promoter CpG methylation (pg 96, line 19), as required by claim 23.

Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the only other identifying characteristic is that agent may be, but is not limited to, those agents that inhibit transcription of one or more ENaC subunit genes, alter the level, amount or activity of a molecule that alters ENaC transcription, alter ENaC RNA stability, and/or alter the trafficking and processing of molecules, for instance, molecules of non-viral origin through intracellular compartments, including without limitation proteasomes, endosomes, and trans-Golgi, and/or through the cytosol, e.g., via cytoskeletal components such as microtubules or microfilaments. In one embodiment, the agent is not an antagonist of ENaC. In another embodiment, the agent is not an agent that binds a cell membrane bound protein, e.g. ENaC or the receptor for hepatocyte growth factor. In yet another embodiment, the agent is not

an agent that alters post-translational processing of ENaC. In another embodiment, the agent is not a gene of, or a gene product encoded by, a mammalian genome, e.g., a protein encoded by a mammalian cell, the complement of the gene, or a portion of the gene or its complement, e.g., an antisense oligonucleotide (pg 4, lines 12-27).

However, the specification does not disclose any identifying characteristic as to how an artisan would have identified and differentiated one structurally and functionally distinct compound that possesses any one of such properties from another compound that might possess such properties. It is noted that all these agents vary greatly in structure and function and therefore each represents a subgenus. Again, the members of any of the subgenuses themselves would have very different structure and the specification does not provide any description of any identifying characteristics of the species of the subgenuses.

In analyzing whether the written description requirement is met for the genus of mammalian cells having aberrant expression or activity of amiloride-sensitive epithelial sodium channels (ENaC) having α, β and γ subunits of ENaC, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the specification discloses cystic fibrosis lung cells (pg 7, line 6) to possess such a property. However, neither the specification nor the art teach the objective, quantitative values to determine whether the expression or activity of the α, β and γ ENaC subunits is aberrant in the enormous genus of mammalian cell types embraced by the claims. Regulation of ENaC activity can occur at different levels, i.e. transcription, translation, translocation and degradation, as well as single-channel open probability and conductance. ENaC subunits [α, β and γ] have been shown to be transcriptionally up-regulated by aldosterone, a low sodium diet or dexamethasone in the kidney, colon and lung, in a tissue- and subunit-specific fashion (Audige et al, Clinical Sci. 104:389-395, 2003; pg. 390, col. 1, ¶2). Using quantitative, real-time polymerase chain reaction (QT-PCR), Audige et al sought to establish whether ENaC is transcriptionally regulated in nephrotic syndrome, and whether expression of ENaC subunit mRNAs and/or protein expression correlates with the profile of urinary sodium excretion using the experimental model of PAN-induced nephrotic syndrome in the rat. Audige et al found that mRNA levels of the α, β and γ ENaC subunits fluctuated over the course of the experiment, first increasing, then decreasing,

having escaped regulation by aldosterone, and that the changes in mRNA levels are not paralleled by the amount of ENaC subunit protein expression, e.g. the abundance of βENaC or γENaC protein did not significantly change throughout the study (pg 393, col. 2, Protein Expression and Discussion). Although significant sodium retention occurred from days 5 to 7 in the presence of high plasma aldosterone concentrations, ENaC mRNAs normalized and protein levels of ENaC subunits remained unchanged (pg 394, col. 1, ¶1).

Similarly, Bubien et al (J. Biol. Chem. 276(11): 8557-8566, 2001) teach that when comparing human lymphocytes from Liddle's disease patients and non-Liddle's disease patients, the Liddle's disease lymphocytes were 2.5 times more fluorescent than non-Liddle's cells when stained for expression of ENaC (pg 8562, col. 1, Immunohistochemical Analysis). However, the authors were unable to ascertain if the increased fluorescence was due to an increase in the amount of ENaC expressed on the cell surface or an increase in the number of exposed epitopes, because the exact number of epitopes and stoichiometry is not known. Bubien et al were unable to provide quantitative values of mRNA or protein expression of the α, β and γ ENaC subunits. ENaC is expressed in the kidney, colon, lung, retina and salivary gland.

The expression of ENaC subunits along the respiratory epithelium is complex and varies between species (Kellenberger et al, Physiological Review 82:735-767, 2002; pg 739, col. 1, Lungs). However, sodium channels, neither known nor contemplated by Applicant yet embraced by the claims, are still being identified in the art and thus the objective states of activity and how such genes are regulated is simply not known. The art teaches that "[O]ur knowledge regarding the structure and function of these [ENaC and ASIC] channels is still emerging and needs to be improved (Kellenberger et al; pg 760, col. 1, Perspectives). Even within the contemplated ENaC α, β and γ genes, the breadth of aberrant expression or activity of these genes is not fully described in the art because the art has not identified quantitative measurements to objectively determine what is "aberrant", especially with respect to the enormous genus of mammalian cell types embraced by the claims.

One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, does not suffice to define the genus because it is only an indication of what the genus does, rather than

what it is. See *Fiers*, 984 F.2d at 1169-71,25 USPQ2d at 1605- 06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such species of the genus may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re *Wilder,* 736 F.2d 1516,1521,222 USPQ 369,372- 73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally thought to exist, in the absence of knowledge as to what that material consists of, is not a description of that entire material.

The Revised Interim Guidelines state:

"The claimed invention as a whole may not be adequately described if the claims require an essential or critical element which is not adequately described in the specification and which is not conventional in the art" (col. 3, page 71434), "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus", "in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (col. 2, page 71436).

An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

Possession may also be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 1 19 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998),

Regents of the University of California v. Eli Lilly, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997)*, *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").

Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. See *Fiers v. Revel*, 25 USPQ2d 1602 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. *In Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Without a correlation between structure and function, the claim does little more than define the claimed invention by function. That is not sufficient to satisfy the written description requirement. *See Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406 ("definition by function ... does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is").

Based on the applicant's specification, the skilled artisan cannot envision the detailed chemical structure of the genus of agents which inhibit expression or activity of amiloride-sensitive epithelial sodium channels (ENaC) having α, β and γ subunits of ENaC, wherein the selected agent is effective to decrease the level or amount of transcription of one or more subunits of ENaC and/or enhances the transduction of a viral gene therapy vector. The one species of agent specifically disclosed, doxorubicin, is not representative of the genus because the genus is highly variant.

Accordingly, given that the specification does not teach what is the complete structure of the agent species of the exceptionally broadly-defined "agent" genus, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that the applicant is in possession of the required starting materials, that is a genus of agents which inhibit expression or

activity of amiloride-sensitive epithelial sodium channels (ENaC) having α, β and γ subunits of ENaC, wherein the selected agent is effective to decrease the level or amount of transcription of one or more subunits of ENaC and/or enhances the transduction of a viral gene therapy vector and/or modulates the transcription of one or molecules that regulates ENaC transcription, to perform the necessary active steps and effect the claimed methods, at the time the application was filed.

Based on the applicant's specification, the skilled artisan cannot envision what mammalian cell expressing amiloride-sensitive epithelial sodium channels (ENaC) having α, β and γ subunits of ENaC would fall within the metes and bounds of the claims for possessing "aberrant expression or activity". Accordingly, given that the specification does not disclose the objective, quantifiable levels by which expression or activity is considered "aberrant", this limited information is not deemed sufficient to reasonably convey to one skilled in the art that the applicant is in possession of the required starting materials, that is a genus of mammalian cells having aberrant expression or activity of amiloride-sensitive epithelial sodium channels (ENaC) having α, β and γ subunits of ENaC, to perform the necessary active steps and effect the claimed methods, at the time the application was filed.

Thus, for the reasons outlined above, it is concluded that the claims do not meet the requirements for written description under 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

4. **Claims 1-2, 4-7, 13, 15-16, 20 and 23 stand rejected under 35 U.S.C. 112, first paragraph**, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

This rejection is maintained for reasons of record in the office action mailed May 21, 2007 and re-stated below. The rejection has been re-worded slightly based upon Applicant's amendment filed August 23, 2007.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention. If not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets

the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (*In re Wands*, 858 F.2d 731, 737, 8 USPQ2ds 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification. Therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention. And thus, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The Breadth of the Claims and The Nature of the Invention

The breadth of the claims is exceptionally large for encompassing an enormous genus of agents that inhibit expression or activity of amiloride-sensitive epithelial sodium channels (ENaC) having α-, β- and γ-subunits of ENaC, wherein the quantitative values by which an artisan would know *a priori* that the expression or activity of the enormous genus of epithelial sodium channels are "aberrant" is neither defined nor disclosed.

The specification does not define the term "mammal", but discloses a preferred mammalian embodiment that is human (pg 4, lines 1-4). The art recognizes mammals to reasonably encompass some 5,500 species (including Humans), distributed in about 1,200 genera, 152 families and up to 46 orders (en.wikipedia.org/wiki/Mammal, last visited March 21, 2007). The art also recognizes that the mammalian body consists of a large genus of distinctly different organs, e.g. heart, lung, brain, muscle, skin, liver, etc.., and an even larger genus of distinctly different cell types. Thus, the claimed inventions reasonably embrace any mammalian cell type that endogenously possesses, or is transformed with a nucleic acid encoding (pg 4, lines 7-8), an epithelial sodium channel.

The claimed inventions are directed to methods for identifying one or more agents with dual therapeutic activity. At issue for the purpose of enablement requirement is:

i) the method step of selecting an agent identified only by it's *a priori* ability to inhibit expression or activity of amiloride epithelial sodium channels (ENaC) having α, β and γ subunits of ENaC and/or enhances the transduction of a viral gene therapy vector and/or modulates the transcription of one or molecules that regulates ENaC transcription, and

ii) the limitation of the mammalian cell having aberrant expression or activity of amiloride-sensitive epithelial sodium channels (ENaC) having α, β and γ subunits of ENaC.

The Existence of Working Examples and The Amount of Direction Provided by the Inventor

With respect to (i), the method comprises the step of selecting one or more agents which inhibits expression or activity of amiloride-sensitive epithelial sodium channels (ENaC) having

α, β and γ subunits of ENaC, wherein the selected agent is effective to decrease the level or amount of transcription of one or more subunits of ENaC and/or enhances the transduction of a viral gene therapy vector and/or modulates the transcription of one or molecules that regulates ENaC transcription.

The elected embodiment of the agent is an antibiotic, specifically doxorubicin. The specification discloses that doxorubicin enhances rAAV transduction and increases the CpG methylation of the γ-ENaC gene promoter (pg 15, Figure 11; pg 83, lines 3-4; pg 93, lines 7-30). It is noted that the specification discloses that it is not known if doxorubicin inhibits long-term ENaC activity through increases in α- or β-ENaC subunit promoter CpG methylation (pg 96, line 19), as embraced by claim 1 and required by claim 23.

With respect to (ii), the method comprises the step of contacting *in vitro* a mammalian cell having aberrant expression or activity of amiloride-sensitive epithelial sodium channels (ENaC) having α, β and γ subunits of ENaC with at least one agent that enhances the transduction of a viral gene therapy vector in mammalian cells and modulates the transcription of one or molecules that regulates ENaC transcription, and identifying an agent, from those agents contacted with the mammalian cells, that alters ENaC expression or activity.

The specification fails to disclose the quantitative values and relationships linking the claimed limitations. There is no definition by which the expression or activity of the genus of claimed sodium channels are to be considered "aberrant", no guidance or direction to the artisan as to the degree by which a disease, including those contemplated by Applicant (pg 9, lines 9-10), is associated with changes in expression or activity of an epithelial sodium channel. The specification fails to disclose the necessary guidance to the artisan for choosing *a priori* an agent that inhibits expression or activity of amiloride-sensitive epithelial sodium channels (ENaC) having α, β and γ subunits of ENaC other than doxorubicin.

The specification broadly discloses that ENaC activity may be inhibited by... altering the trafficking and processing of molecules through intracellular compartments, including without limitation proteasomes, endosomes, and trans-Golgi, and/or through the cytosol, e.g., via cytoskeletal components such as microtubules and microfilaments (pg 17, lines 1-8). Applicant further contemplates that altering ENaC activity may be accomplished by decreasing ENaC

transcription via direct interaction with the promoter of one or more ENaC subunits, e.g. methylation or a repressor (pg 17, lines 10-21).

The State of the Prior Art

Epithelial Sodium Channels

The specification does not define the term "epithelial sodium channels", and thus the claimed subject matter reasonably embraces any sodium channel expressed in epithelial cells. In the absence of a definition, the specification discloses prior art to identify the claimed subject matter (pg 1, line 24; Stutts et al, J. Biol. Chem. 272(22):14037-14040, 1997; Donaldson et al, J. Biol. Chem. 277(10):8338-8345, 2002 *of record), wherein the art teaches that ENaC is an acronym for amiloride-sensitive epithelial sodium channel, comprising α, β and γ subunits (pg 14037). However, the claimed genus of epithelial sodium channels reasonably embraces sodium channels neither disclosed nor contemplated by Applicant. For example, Schaefer et al and Sakai et al (FEBS Letters 471:205-210, 2000; J. Physiol 519:323-333, 1999) teach the identification of a novel amiloride-sensitive cation channel 5 that is expressed in the epithelia of the small intestine.

The art teaches that epithelial sodium channel (ENaC; found in databanks under SCA, for "sodium channel, amiloride-sensitive, and SCNN1, "sodium channel, non-neuronal) is a class of ion channels that was discovered at the beginning of the 1990s (Kellenberger et al, Physiological Review 82:735-767, 2002; pg 735-736, joining ¶). The first draft sequence of the human genome reveals the presence of α-, β-, γ- and δ-ENaC proteins (pg 737, col. 2, ¶1). ENaC is expressed in the kidney, colon, lung, and salivary gland (pg 737, col. 2). In mammals, the three ENaC subunits (α, β, γ) are expressed in keratinocytes of all epidermal layers (pg 739, col. 2, ¶3). ENaC transcripts can also be found in the pluristratified epithelium of the esophagus where ENaC's role is unknown. The expression of ENaC subunits along the respiratory epithelium is complex and varies between species (pg 739, col. 1, Lungs). Finally, salt taste is transduced by direct amiloride-sensitive influx of Na+ in the taste cells of the fungiform papillae of the anterior part of the tongue, suggesting the presence of an amiloride-sensitive Na+ channel (pg 739, col. 2, ¶4); however, the specific role of ENaC in salty taste transduction still remains to be clearly demonstrated. The δ-ENaC subunit is expressed in testis, ovary, pancreas, and to a lesser extent in brain and heart (pg 740, col. 1, Other Tissues). ENaC transcripts and proteins were detected in retina photoreceptors, but ENaC's role in phototransduction remains to be established.

Aberrant Expression or Activity

With respect to the limitation regarding "aberrant expression or activity", the art does not teach the objective, quantitative values to determine whether the expression or activity of the α, β and γ ENaC subunits is aberrant in the enormous genus of mammalian cell types embraced by the claims. Regulation of ENaC activity can occur at different levels, i.e. transcription, translation, translocation and degradation, as well as single-channel open probability and conductance. ENaC subunits [α, β and γ] have been shown to be transcriptionally up-regulated by aldosterone, a low sodium diet or dexamethasone in the kidney, colon and lung, in a tissue- and subunit-specific fashion (Audige et al, Clinical Sci. 104:389-395, 2003; pg. 390, col. 1, ¶2). Using quantitative, real-time polymerase chain reaction (QT-PCR), Audige et al sought to

establish whether ENaC is transcriptionally regulated in nephrotic syndrome, and whether expression of ENaC subunit mRNAs and/or protein expression correlates with the profile of urinary sodium excretion using the experimental model of PAN-induced nephrotic syndrome in the rat. Audige et al found that mRNA levels of the α, β and γ ENaC subunits fluctuated over the course of the experiment, first increasing, then decreasing, having escaped regulation by aldosterone, and that the changes in mRNA levels are not paralleled by the amount of ENaC subunit protein expression, e.g. the abundance of βENaC or γENaC protein did not significantly change throughout the study (pg 393, col. 2, Protein Expression and Discussion). Although significant sodium retention occurred from days 5 to 7 in the presence of high plasma aldosterone concentrations, ENaC mRNAs normalized and protein levels of ENaC subunits remained unchanged (pg 394, col. 1, ¶1).

Similarly, Bubien et al (J. Biol. Chem. 276(11): 8557-8566, 2001) teach that when comparing human lymphocytes from Liddle's disease patients and non-Liddle's disease patients, the Liddle's disease lymphocytes were 2.5 times more fluorescent than non-Liddle's cells when stained for expression of ENaC (pg 8562, col. 1, Immunohistochemical Analysis). However, the authors were unable to ascertain if the increased fluorescence was due to an increase in the amount of ENaC expressed on the cell surface or an increase in the number of exposed epitopes, because the exact number of epitopes and stoichiometry is not known. Bubien et al were unable to provide quantitative values of mRNA or protein expression of the α, β and γ ENaC subunits.

The Level of One of Ordinary Skill and The Level of Predictability in the Art

The level of one of ordinary skill in the clinical and cell biological arts is considered to be high. However, sodium channels, neither known nor contemplated by Applicant yet embraced by the claims and expressed in epithelial cells, are still being identified in the art and thus the objective states of activity and how such genes are regulated is simply not known. The art teaches that "[O]ur knowledge regarding the structure and function of these [ENaC and ASIC] channels is still emerging and needs to be improved (Kellenberger et al; pg 760, col. 1, Perspectives). Inherited human diseases cause by the ENaC family members hINAC and ASICs have not been identified to date (Kellenberger et al; pg 760, col. 2, last ¶). Even within the contemplated ENaC α, β and γ genes, the breadth of disease states and symptoms thereof caused by aberrant expression or activity of these genes is not fully described in the art because the art has not identified quantitative measurements to objectively determine what is "aberrant", especially with respect to the enormous genus of mammalian cell types embraced by the claims. Thus, one of ordinary skill in the art would reasonably conclude a significant degree of unpredictability regarding an artisan to *a priori* identify a mammalian cell having aberrant expression or activity of amiloride-sensitive epithelial sodium channel proteins.

The Quantity of Any Necessary Experimentation to Make or Use the Invention

Given the absence of definitions and the lack of disclosure, the specification fails to provide the necessary guidance and direction so that an artisan would know *a priori* that a particular agent has the required inherent property of inhibiting expression or activity of amiloride-sensitive epithelial sodium channels (ENaC) having α, β and γ subunits of ENaC,

wherein the selected agent is effective to decrease the level or amount of transcription of one or more subunits of ENaC and/or enhance transduction of a viral gene therapy vector, so as to perform the method steps as claimed. The artisan must first select an agent and then test the agent to determine whether or not it possesses all of the recited limitations before proceeding with the method step of contacting a mammalian cell. Similarly, the specification fails to provide the necessary guidance and direction so that an artisan would know *a priori* that a mammalian cell possesses the inherent property aberrant expression or activity of amiloride-sensitive epithelial sodium channels (ENaC) having α, β and γ subunits of ENaC, so as to perform the method steps as claimed.

The courts have stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in patent application. 27 USPQ2d 1662 *Exparte Maizel.* In the instant case, in view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

Applicant's Arguments

Applicant argues that:

a) it is well-settled that it is not necessary that a patent applicant have prepared and tested all the embodiments of his invention in order to meet the requirements of §112. Furthermore, enablement is not precluded by the necessity for some experimentation, such as routine screening. The key word is "undue" not "experimentation." The specification discloses methods that provide objective, quantitative values on relative expression or activity of the α, β and γ ENaC subunits.

b) the specification discloses how to test for agents that have the recited dual activities.

c) it is Applicant's position that it is well within the skill of the art worker to compare test values to control values to determine whether the test values are substantially the same or different, e.g., "aberrant", than the control values.

Applicant's argument(s) has been fully considered, but is not persuasive.

With respect to a), as *In re Gardner, Roe and Willey*, 427 F.2d 786,789 (C.C.P.A. 1970), the skilled artisan might eventually find out how to use the invention after "a great deal of work". In the case of *In re Gardner, Roe and Willey*, the invention was a compound which the inventor claimed to have antidepressant activity, but was not enabled because the inventor failed to disclose how to use the invention based on insufficient disclosure of effective drug dosage. The court held that "the law requires that the disclosure in the application shall inform them how to use, not how to find out how to use for themselves". The courts have stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in patent application. 27 USPQ2d 1662 *Exparte Maizel*. In the instant case, and in view of the lack of disclosure in the instant specification, the artisan would essentially have to invent for him or herself the instantly claimed methods by having to first screen an enormous genus of structurally distinct hypothetical compounds to first ascertain whether or not such compounds possess the required functional property recited in claims 1(a), 2(a), 7 and 23.

With respect to b), Applicant has not addressed the substantive issue. Specifically, how the artisan would know *a priori* that a particular agent would possess the functional property of inhibiting the expression or activity of the genus of amiloride-sensitive epithelial sodium channels (ENaC) having α, β and γ subunits of ENaC known, and not yet known, in the art. Sodium channels of the ENaC gene family are still being identified in the art and thus the objective states of activity and how such genes are regulated are simply not known. The art teaches that "[O]ur knowledge regarding the structure and function of these [ENaC and ASIC] channels is still emerging and needs to be improved (Kellenberger et al; pg 760, col. 1, Perspectives). While doxorubicin is disclosed to possess the claimed functional properties, neither the claims, the specification, nor Applicant's amendment provide a nexus between doxorubicin and the enormous claimed genus of agents. In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

With respect to c), the specification discloses that doxorubicin increases the CpG methylation of the γ-ENaC gene promoter (pg 15, Figure 11; pg 93, lines 7-30). It is noted that the specification discloses that it is not known if doxorubicin inhibits long-term ENaC activity

through increases in α- or β-ENaC subunit promoter CpG methylation (pg 96, line 19), as required by claim 23

The claims embrace an enormous genus of mammalian cells, each possessing *a priori* aberrant expression or activity of amiloride-sensitive epithelial sodium channels (ENaC) having α, β and γ subunits of ENaC. While applicant argues that objective, quantitative values on relative expression or activity of the α, β and γ ENaC subunits are disclosed, in the absence of explicitly pointing out where (page, line) the limitations are taught, the instant argument is incomplete and unpersuasive. Furthermore, Applicant does not provide a nexus between the instantly disclosed α, β and γ ENaC subunits and the expression or activity of other members of the epithelial sodium channels (ENaC) gene family. Thus, applicant's argument is not commensurate in scope to the claimed method.

The art teaches that ENaC family members are still being identified in the art and thus the objective states of activity and how such genes are regulated are simply not known. The art teaches that "[O]ur knowledge regarding the structure and function of these [ENaC and ASIC] channels is still emerging and needs to be improved (Kellenberger et al; pg 760, col. 1, Perspectives). It is the examiner's position that the claimed invention is not enabled for the breadth of the claimed ENaC gene family because neither the art nor the specification teaches what degree of expression or activity is to be considered "aberrant".

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his invention.

5. **Claims 1-2, 4-7, 13, 15-16, 20 and 23 are rejected under 35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

With respect to claims 1 and 2 (and dependent claims), the claims are vague in that no step(s) in the claimed methods refers back to or recapitulates the preamble of the independent claims. Applicants recite methods of identifying one or more agents with dual therapeutic activity, but no step is recited that actually accomplishes the preamble. Dependent claims are

included in the basis of the rejection because it is unclear if additional, undisclosed steps are a part of the claimed method, and therefore the metes and bounds of the claimed subject matter are unclear.

With respect to claim 20, the claim recites a trademarked product, DOXIL®. If the trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of the 35 U.S.C. 112, second paragraph. *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. In fact, the value of a trademark would be lost to the extent that it became descriptive of a product, rather than used as an identification of a source or origin of a product. Thus, the use of a trademark or trade name in a claim to identify or describe a material or product would not only render a claim indefinite, but would also constitute an improper use of the trademark or trade name. See MPEP 2173.05(u).

Examiner's Note

The Examiner is aware of the apparent contradiction between applying the 35 U.S.C. 112, first paragraph, lack of enablement rejection presented above and the following 35 U.S.C. 103 art rejections. For the sake of compact prosecution, all issues relating to the instant application will be set forth. The art rejections are applied for disclosing knowledge in the art prior to the filing of the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. **Claims 1, 4-5, 13, 15-16, 20 and 23 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Schwarzbach et al (Int. J. Oncology 20: 1211-1218, 2002; *of record) in view of Duan et al (J. Clin. Invest. 105:1573-1587, 2000; *of record) and Bruno et al (FEBS Letters 427:241-246, 1998), as evidenced by Kiyomiya et al (Int. J. Oncol. 20(6):1205-1209, 2002; *of record in IDS).

Schwarzbach et al teach a method of identifying an agent with dual therapeutic activity, the method comprising the step of selecting the antibiotic "agent" doxorubicin (pg 1212, Materials and Methods), and administering the doxorubicin and the gene therapy vector AAV-2 to human cells, wherein AAV-2 infection is known in the art to sensitize cells to chemotherapy-based genotoxic treatment and the administration of doxorubicin enhanced the effect of the AAV-2, namely increased cell killing (e.g., pg 1213, Figure 1).

With respect to the limitation that the agent enhance transduction of the viral gene therapy vector, the specification discloses that, for AAV the [transduction] process includes 1) endocytosis of the AAV after it has bound to a cell surface receptor, 2) escape from endosomes or other intracellular compartments in the cytosol of a cell, 3) trafficking of the viral particle or viral genome to the nucleus, 4) uncoating of the virus particles, and generation of expressible double stranded AAV genome forms, including circular intermediates (pg 19, lines 2-7). Scwharzbach et al do not explicitly teach that doxorubicin has the functional property to enhance transduction of the viral vector. However, at the time of the invention, Duan et al taught that proteasome modulating agents, e.g. LLnL, enhanced rAAV transduction of mammalian lung epithelial cells, wherein the rAAV comprised a marker gene (pg 1576, Figure 5).

Duan et al did not teach doxorubicin to have the functional property of enhancing rAAV transduction. However, at the time of the invention, Kiyomiya et al taught that adriamycin (a synonym for doxorubicin) is a proteasome protease inhibitor in the same genus of proteasome inhibitors that enhance rAAV transduction. Thus, absent evidence to the contrary, one of ordinary skill in the art would reasonably expect doxorubicin to enhance rAAV transduction because it is another species within the genus of proteasome inhibitors recognized in the art to

possess rAAV transduction enhancement properties. There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure *at the time of invention*, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003) Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). In the instant case, Schwarzbach et al teach that a combination of doxorubicin and AAV-2 infection improves the therapeutic efficiency (pg 1212, col. 1, ¶1), and thus, absent evidence to the contrary, the doxorubicin enhanced AAV transduction.

Schwarzbach et al do not teach the mammalian cells to have aberrant expression or activity of epithelial sodium channels. However, the specification fails to disclose or define the quantitative values by which the expression or activity of the claimed sodium channels are to be considered "aberrant". Thus, absent evidence to the contrary, the cells of the cited have some degree of aberrant expression or activity of the claimed sodium channels.

Schwarzbach et al do not teach that doxorubicin may modulate the transcription or activity of one or more subunits of ENaC or one or molecules that regulate ENaC transcription. However, absent evidence to the contrary, nothing non-obvious is seen with the claimed limitations that the agent, specifically doxorubicin, possess the property of decreasing the level or amount of transcription of one or more subunits of ENaC or a molecule that regulates ENaC transcription because prior to the invention, Bruno et al taught that doxorubicin was known in the art to broadly affect the transcriptional machinery, e.g. RNA Polymerase II, the major RNA polymerase responsible for transcribing genes whose RNAs will be translated into proteins, e.g. one or more subunits of ENaC, as well as impairing the function of several known genes at the transcriptional level (pg 245, col. 1, ¶1). "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). The art had long-recognized doxorubicin to affect the cellular transcriptional machinery, and the instant claims do not recite the degree to which the level of transcription is to be modulated or decreased. In light of the art-recognized property that doxorubicin impairs the transcriptional machinery, one of ordinary skill

in the art would reasonably expect doxorubicin to modulate the transcription or activity of one or more subunits of ENaC or one or molecules that regulate ENaC transcription.

The practice of identifying agents that have dual activity, consciously or subconsciously, so as to improve a desired result was common in the art prior to the invention. Schwarzbach et al teach a method to identify agents that improve the therapeutic efficiency, with emphasis on the combination of doxorubicin and AAV-2 infection. Bruno et al teach that the art-recognized antibiotic and proteasome inhibitor doxorubicin has dual activity by affecting the transcription of a multitude of genes. And, Duan et al teach that the genus of proteasome inhibitors to which doxorubicin belongs also have dual activity to enhance viral transduction. It would have been obvious to one of ordinary skill in the art to apply the method of infecting human cells with AAV vectors in combination with incubation in the presence of doxorubicin as taught by Schwarzbach et al to mammalian lung epithelial cells as taught by Duan et al to identify an agent with dual therapeutic activity with a reasonable chance of success because all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. An artisan would be motivated to infect human lung cells with AAV vectors in combination with incubation in the presence of doxorubicin because strategies to treat cystic fibrosis comprising the use of viral gene therapy vectors were known in the art, Duan et al teach that art-recognized proteasome inhibitors provide new approaches to circumvent infection barriers for gene therapy of diseases such as cystic fibrosis and Schwarzbach et al teach that a combination of doxorubicin and gene therapy vectors such as AAV-2 infection improves the therapeutic efficiency.

Thus, the invention as a whole is *prima facie* obvious.

7. **Claims 2, 4, 6-7, 13, 15-16, 20 and 23 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Schwarzbach et al (Int. J. Oncology 20: 1211-1218, 2002; *of record) in view of Duan et al (J. Clin. Invest. 105:1573-1587, 2000; *of record), Bruno et al (FEBS Letters 427:241-246, 1998) and Johnson et al (Nature Genetics 2: 21-25, 1992), as evidenced by Kiyomiya et al (Int. J. Oncol. 20(6):1205-1209, 2002; *of record in IDS).

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430, 433 (CCPA 1977). In the instant case, Schwarzbach et al teach that a combination of doxorubicin and AAV-2 infection improves the therapeutic efficiency (pg 1212, col. 1, ¶1), and thus, absent evidence to the contrary, the doxorubicin enhanced AAV transduction.

Schwarzbach et al do not teach the mammalian cells to have aberrant expression or activity of epithelial sodium channels. However, the specification fails to disclose or define the quantitative values by which the expression or activity of the claimed sodium channels are to be considered "aberrant". Thus, absent evidence to the contrary, the cells of the cited have some degree of aberrant expression or activity of the claimed sodium channels.

Schwarzbach et al do not teach that doxorubicin may modulate the transcription or activity of one or more subunits of ENaC or one or molecules that regulate ENaC transcription. However, absent evidence to the contrary, nothing non-obvious is seen with the claimed limitations that the agent, specifically doxorubicin, possess the property of decreasing the level or amount of transcription of one or more subunits of ENaC or a molecule that regulates ENaC transcription because prior to the invention, Bruno et al taught that doxorubicin was known in the art to broadly affect the transcriptional machinery, e.g. RNA Polymerase II, the major RNA polymerase responsible for transcribing genes whose RNAs will be translated into proteins, e.g. one or more subunits of ENaC, as well as impairing the function of several known genes at the transcriptional level (pg 245, col. 1, ¶1). "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). The art had long-recognized doxorubicin to affect the cellular transcriptional machinery, and the instant claims do not recite the degree to which the level of transcription is to be modulated or decreased. In light of the art-recognized property that doxorubicin impairs the transcriptional machinery, one of ordinary skill in the art would reasonably expect doxorubicin to modulate the transcription or activity of one or more subunits of ENaC or one or molecules that regulate ENaC transcription.

Neither Schwarzbach et al nor Duan et al disclose the method step of identifying an agent that alters ENaC expression or activity. However, at the time of the invention, Johnson et al taught that in cystic fibrosis, amiloride abolishes Na+ transport but no Cl- secretion is induced; whereas, in normal or corrected epithelia, amiloride abolishes Na+ transport and Cl- secretion is

induced (pg 21, col. 2). Thus, the degree of CFTR correction in a mammalian lung cell or population of cells having aberrant expression or activity of amiloride-sensitive epithelial sodium channel (ENaC) having α, β and γ subunits transduced with a viral gene therapy vector encoding a functional CFTR gene may be quantified by assaying the percent inhibition of the basal short circuit current (Isc) of the amiloride-sensitive epithelial sodium channel (ENaC) (Johnson et al, entire paper).

The practice of identifying agents that have dual activity, consciously or subconsciously, so as to improve a desired result was common in the art prior to the invention. Schwarzbach et al teach a method to identify agents that improve the therapeutic efficiency, with emphasis on the combination of doxorubicin and AAV-2 infection. Duan et al teach that the genus of proteasome inhibitors to which doxorubicin belongs also have dual activity to enhance viral transduction. And, Bruno et al teach that the art-recognized antibiotic and proteasome inhibitor doxorubicin has dual activity by affecting the transcription of a multitude of genes. It would have been obvious to one of ordinary skill in the art to combine the method of Schwarzbach et al to test *in vitro* for a pharmaceutical composition comprising doxorubicin and a viral gene therapy vector encoding a therapeutic gene, e.g. CFTR, to achieve the desired therapeutic activity with the method of Johnson et al to assay the percent inhibition of the basal short circuit current (Isc) of the amiloride-sensitive epithelial sodium channel (ENaC) as a measurement of the degree of CFTR correction in a cell or population of cells transduced with a viral gene therapy vector with a reasonable chance of success because all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to the ordinary artisan. An artisan would be motivated to measure ENaC expression or activity because the art recognized that assaying the percent inhibition of the basal short circuit current (Isc) of the amiloride-sensitive epithelial sodium channel (ENaC) was common means of measuring CFTR correction.

Thus, the invention as a whole is *prima facie* obvious.

Conclusion

8. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kevin K. Hill, Ph.D. whose telephone number is 571-272-8036. The examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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